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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 07/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,957	YUAN ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *2,3,7,8,20-29 and 40-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13 and 30-39* is/are rejected.

7)☒ Claim(s) *4-6,9-12 and 14-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-45 are pending.

Election/Restrictions

2. In response to the restriction requirement mailed on .May 14, 2004, Applicants elect the claims of Group I, i.e., claims 4-6, 9-19, and 30-39 in part, and elect schizophrenia as the species for the method claims. Claims of Groups II to VII are withdrawn from further consideration as being drawn to the non-elected invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 13, 30-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1,

- Definitions of W, R6, the meaning of 'aromatic ring' is unclear. The metes and bounds can not be ascertained from the definition (pages 12-13 of the specification) that 'aromatic' is meant both aryl and heteroaryl, and 'heteroaryl is meant '*one or more* aromatic ring system of 5-7-membered rings containing at least one and up to 4 hetero atoms'
- Definition of W, the meaning of 'any heterocycle having aromatic character' is unclear. The metes and bounds can not be ascertained from the definition (pages 12-13 of the specification) that it is meant the 'heteroaryl groups described above and also bicyclic ring systems where at least one of the ring is aromatic', as there is no description of 'the other ring' in the specification.

- Definition of R6 and R7 together form a 5-8-membered ring is unclear as to the meaning of 'contains a fused aryl as part of the 5-8 membered ring'. Does applicant intend the 5-8 memebered ring further fused to an aryl or the fused ring, including the aryl, has 5-8 members? A full definition of the fused ring is not found in the specification.
- Definition of R6 and R8 together form a 5-8-membered ring is unclear as to the meaning of 'contains a fused aryl as part of the 5-8 membered ring'. Does applicant intend the 5-8 memebered ring further fused to an aryl or the fused ring, including the aryl, has 5-8 members? A full definition of the fused ring is not found in the specification.
- Definition of R6, it is unclear whether the alkyl is optionally only substituted with an aromatic ring or it is also optionally substituted with other substituents because some of the examples, such as the last compound on page 26 of the specification, have cycloalkyl substituted alkyl. See paragraph d below.

b. Claim 30, the stereoisomeric forms of the compound of claim 1 have no antecedent basis in claim 1.

c. Claims 34, 35 provide for the use of the compound, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

d. Claim 13, some of the compounds, such as the first two compounds having cyclohexyl or cyclopentyl on the respective methyl and ethyl as R6, and the 7^{th} to 9^{th} compounds, wherein the tetrahydroisoquinoline has a cycloalkyl as a substituent, have no antecedent in the base claim 1.

The rejection is applicable to claims dependent on the above claims.

Claim Rejections - 35 USC § 101

4. Claims 34, 35 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Duplicate Claims

5. Claim 31 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. The recited use in claim 31 does not further limit the compound of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33, 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The disease or disorder associated with pathogenic neurokinin-3 receptor activation reaches out to as yet unidentified diseases/disorders, the description of which is not found in the specification. The nexus between binding to the NK3 receptor and the treatment of any or all of the diseases/disorders, such as schizophrenia, has not been adequately described in the specification.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 30-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, is only enabling for making and using the compounds the compounds wherein W is phenyl, X is dihydroimidazolyl, or X is C(O)NR6R7 wherein R6 is alkyl substituted with optionally substituted phenyl, or R6 and R7 together form a 6-membered ring fused to a benzene to form a tetrahydroisoquinoline, as exemplified in claims 4-6, 9-19, for treating pain or chronic pulmonary obstructive disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

a. *Nature of the invention.*

The instant invention is drawn to a NK3 receptor antagonist compound for treating or preventing a disease or disorder associated with pathogenic neruokinin 3 receptor activation, such as the diseases/disorders as recited on page 3 of the specification.

b. *State of the prior art /level of the skill in the art.*

The human NK3 receptor has been cloned and expressed in 1992. The first non-peptide neurokinin-3 receptor antagonist was described in 1995 (Gao, Current Medicinal Chemistry, 1999, 6, 375-388, page 385, compound 30). Although different diseases are implicated with the neurokinin receptors, the exact roles of neurokinin-3 receptors have not been fully determined (page 376). The nexus between binding to the NK3 receptor and the treatment of any or all of the diseases/disorders as recited has not been fully established.

While some of the diseases/disorders recited may be treatable, prevention of these diseases/disorders is not feasible since the criteria for determining the subjects at risk have not been determined.

The level of the skilled artisan in the neurokinin receptor art is high.

c) *The predictability/unpredictability of the art.*

The high degree of unpredictability is well-recognized in the neruokinin receptor art. A slight change in the structure of the compound would drastically change its biological activity and selectivity as evidenced in the different IC_{50} values for the various structurally similar neurokinin receptor antagonist compounds (Gao, pages 385-6, Tables 8, 9). One of ordinary skill in the art would therefore have little basis to extrapolate the test results to compounds of dissimilar structures.

d) *The amount of direction presented/working examples.*

How to make

Preparation of example compounds is limited to compounds wherein W is phenyl, X is dihydroimidazolyl, or X is C(O)NR6R7 wherein R6 is alkyl substituted with optionally substituted phenyl, or R6 and R7 together form a 6-membered ring fused to a benzene to form a tetrahydroisoquinoline.

Starting material and the process of making the instantly claimed compounds other than the example compounds, especially compounds wherein W is other than phenyl, especially those wherein R6 and R8 form a 5-8 memebered ring, optionally further fused with other ring (s) , or R6 and R7 form a 5, 7, 8 membered ring, optionally further fused with other ring(s), which are not fully described in the specification, are not seen but required. Sources are particularly pertinent especially when the structures of these compounds are not described. Absent sources, the public is offered mere language, rather than enablement. Ex parte Moersch 104 USPQ 122. In re Howarthe 210 USPQ 689.

How to use

The procedure for NK3 receptor binding assay is described on page 52 and the results shown for compounds 1-3 on page 53. No in vivo procedures are described.

e) *The breadth of the claims.*

Applicant's assertion that all the structurally diverse compounds with structures far removed from the example compounds would be effective in treating or preventing any disease or disorder associated with pathogenic neruokinin 3 receptor activation as recited on page 3 of the specification, such as schizophrenia, do not commensurate with the scope of the objective enablement, especially in view of the non-establishment of the nexus between the binding to the

NK3 receptor and any or all of the diseases, the high degree of unpredictability and the limited working examples (paragraphs b) to d) above).

f) *Quantitation of experimentation necessary.*

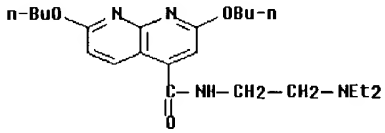
Since insufficient teaching and guidance have been provided in the specification (paragraphs b) to f) above), one of ordinary skill in the art, even with high level of skill, would not be able to use all the compounds as claimed without undue experimentation except for using the compounds wherein W is phenyl, X is dihydroimidazolyl, or X is C(O)NR6R7 wherein R6 is alkyl substituted with optionally substituted phenyl, or R6 and R7 together form a 6-membered ring fused to a benzene to form a tetrahydroisoquinoline for treating pain or chronic pulmonary obstructive disorder.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Burckhardt (DE 829894, abstract). Assuming that alkyl of R6 is optionally substituted (see paragraph 3a above), the following compound is encompassed by the instant claim.



Allowable Subject Matter

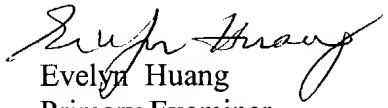
9. Claims 4-6, 9-12, 14-19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Giardina (WO 97/19926, PTO-1449) discloses a quinoline-4-carboxamide compound as NK-2 receptor antagonists. The instant is a napthridine-4-carboxamide compound with NK-3 receptor antagonizing activity. Motivation to modify Giardina's compound to arrive at the instant is lacking.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Evelyn Huang
Primary Examiner
Art Unit 1625